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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/561,092	05/25/2006	Steven F. Dowdy	034123-199	9450

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BUCHANAN, INGERSOLL & ROONEY LLP
P.O. BOX 1404
ALEXANDRIA, VA 22313-1404

EXAMINER	
DESAI, ANAND U	
ART UNIT	**PAPER NUMBER**
1656	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/07/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/561,092	DOWDY ET AL.	
	Examiner	Art Unit	
	Anand U. Desai, Ph.D.	1656	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 December 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *5,7-10 and 20-30* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6,11-19 and 31-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *20050221; 20060731*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

1. Applicant's election without traverse of Group I, drawn to claims 1-19, and 31-35 in the reply filed on December 12, 2006 is acknowledged. Applicant's election of the species of TAT protein as set forth in claims 2 and 32, the species SV40 large T antigen as set forth in claim 12, and the species of peptide analogs of influenza virus hemagglutinin as set forth in claims 13 and 34 is acknowledged.

2. Claims 5, 7-10, and 20-30 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species and inventions, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on December 12, 2006.

3. Claims 1-4, 6, 11-19, and 31-35 are currently under examination.

Priority

4. Acknowledgment is made of applicant's claim for priority under 35 U.S.C. 119(e). The priority date is June 20, 2003.

Information Disclosure Statement

5. The information disclosure statements (IDSs) submitted on February 21, 2005 and July 31, 2006 have been considered by the examiner.

Claim Rejections - 35 USC § 112, First Paragraph, Written Description

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

7. Claims 1-4, 6, 11-19, 32, and 33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are rejected under 35 U.S.C. 112, first paragraph, written description, because the disclosure does not direct one of ordinary skill in the art to the genus of protein transduction moieties that can be conjugate to the genus of heterologous polypeptides, or a genus of protein transduction moieties that can be conjugated to the genus of fusogenic polypeptides. Claim 32 is rejected under 35 U.S.C. 112, first paragraph, written description, because the disclosure does not direct one of ordinary skill in the art to the functional fragments of protein transduction moieties that can be conjugated to the fusogenic domain and retain activity.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, Paragraph 1, "Written Description" Requirement, published at Federal Register, Vol. 66, No. 4, pp. 1099-1111 outline the method of analysis of claims to determine whether adequate written description is present. The first step is to determine what the claim as a whole covers, i.e., discussion of the full scope of the claim. Second, the application should be fully reviewed to understand how applicant provides support for the claimed invention including each element and/or step, i.e., compare the scope of the claim with the scope of the description. Third, determine whether the applicant was in possession of the claimed invention as a whole at the time of filing. This should include the following considerations: (1) actual reduction to practice, (2) disclosure of drawings or structural chemical formulas, (3) sufficient relevant identifying

characteristics such as complete structure, partial structure, physical and/or chemical properties and functional characteristics when coupled with a known or disclosed correlation between function and structure, (4) method of making the claimed invention, (5) level of skill and knowledge in the art and (6) predictability of the art. For each claim drawn to a single embodiment or species, each of these factors is to be considered with regard to that embodiment or species. For each claim drawn to a genus, each of these factors is to be considered to determine whether there is disclosure of a representative number of species that would lead one skilled in the art to conclude that applicant was in possession of the claimed invention. Where skill and knowledge in the art is high adequate written description would require fewer species to be disclosed than in an art where little is known; further, more species would need to be disclosed to provide adequate written description for a highly variable genus.

First, what do the claims as a whole cover? The claims are directed to a composition comprising a first fusion polypeptide comprising a first domain comprising a protein transduction moiety, the transduction moiety comprising a membrane transport function, and the second domain comprising a heterologous polypeptide, and a second fusion polypeptide comprising a first domain comprising a protein transduction moiety, the transduction moiety comprising a membrane transport function and the second domain comprising a fusogenic polypeptide. The claims are also directed to a fusion polypeptide comprising a protein transduction domain and a fusogenic peptide.

Second, how does the scope of the claims compare to the scope of the disclosure?

The scope of the claim is broader than the scope of the disclosure. The claims are directed to any protein transduction domain conjugates with any fusogenic-protein transduction

domain conjugates. The disclosure describes the use of a Tat protein transduction domain species conjugated to a Cre recombinase protein. The disclosure describes the use of a HA_2-Tat (fusogenic-protein transduction domain) conjugate. The composition comprising both polypeptide conjugates is used to describe the facilitated release of Cre-recombinase conjugate from endosomal vesicles. The Cre recombinase conjugate displays higher enzymatic activity when present with the fusogenic conjugate polypeptide.

Third, the factors need to be considered.

(1) What was actually reduced to practice?

The method using the specific species, comprising Tat transduction domain conjugated to Cre recombinase and the use of HA_2-Tat (fusogenic-protein transduction domain) conjugate shown was actually reduced to practice.

(2) Is there disclosure of drawings or structural chemical formulas?

The structural chemical formula is given for the specific individual species, but a representative number of conjugated species are not described. There is no disclosure of how any particular structure is correlated to the function of the conjugate envisioned.

(3) Are there sufficient relevant identifying characteristics disclosed?

There are insufficient relevant identifying characteristics disclosed (see knowledge in the art below).

(4) Is there at least one method of making the claimed invention disclosed?

Peptide synthesis techniques can be used to make the claimed invention.

(5) What is the level of skill in the art and what knowledge is present in the art?

The level of skill in the art of protein chemistry is high, about that of a PhD scientist with several years' experience.

Violini et al. describe the permeation barrier of Tat-peptides in well-differentiated epithelial cells. The Tat-conjugated peptides bind to the membrane but do not translocate through the membrane (see entire document, particularly last sentence of Abstract).

Falnes et al. describe the ability of Tat and VP22 protein transduction domain peptides to bind to the membrane surface, but not translocating the membrane bilayer (see page 4352, Figure 2, lack of toxicity for dtA when conjugated to Tat or VP22 protein transduction domain).

(6) What is the level of predictability of the art?

The level of predictability in this art is very low since, there is no information upon which to base a prediction of what molecules can be conjugated and still retain function.

Thus, having analyzed the claims with regard to the Written Description guidelines, it is clear that the specification does not disclose a representative number of species which would lead one skilled in the art to conclude that applicant was in possession of the claimed invention.

Claim Rejections - 35 USC § 112, First Paragraph, Enablement

8. Claims 1-4, 6, 11-19, 32, and 33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the conjugates disclosed in the examples, does not reasonably provide enablement for any conjugates as currently claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The claims are rejected because of undue experimentation to practice the claimed method for the genus of protein transduction moieties, the heterologous polypeptides conjugated with the protein transduction moieties, the fusion polypeptide comprising the genus of protein transduction moieties conjugated to the genus of fusogenic polypeptides. The undue experimentation arises due to the unpredictability based on the different structures of the peptides.

In *In re Wands*, 8 USPQ2d 1400 (Fed. Cir., 1988) eight factors should be addressed in determining enablement.

While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims. This can be done by making specific findings of fact, supported by the evidence, and then drawing conclusions based on these findings of fact. For example, doubt may arise about enablement because information is missing about one or more essential parts or relationships between parts which one skilled in the art could not develop without undue experimentation. In such a case, the examiner should specifically identify what information is missing and why one skilled in the art could not supply the information without undue experimentation. See MPEP § 2164.06(a). References should be supplied if possible to support a prima facie case of lack of enablement, but are not always required. *In re Marzocchi*, 439 F.2d

220, 224, 169 USPQ 367, 370 (CCPA 1971). However, specific technical reasons are always required.

1) The nature of the invention: the instant claims are directed to a composition comprising a first fusion polypeptide comprising a first domain comprising a protein transduction moiety, the transduction moiety comprising a membrane transport function, and the second domain comprising a heterologous polypeptide, and a second fusion polypeptide comprising a first domain comprising a protein transduction moiety, the transduction moiety comprising a membrane transport function and the second domain comprising a fusogenic polypeptide. The claims are also directed to a fusion polypeptide comprising a protein transduction domain and a fusogenic peptide.

3) The predictability or unpredictability of the art: & 6) The quantity of experimentation necessary: & 7.) The state of the prior art: the prior art has shown a large quantity of experimentation is often necessary to determine the functional effects on proteins after structural alterations.

Violini et al. describe the permeation barrier of Tat-peptides in well-differentiated epithelial cells. The Tat-conjugated peptides bind to the membrane but do not translocate through the membrane (see entire document, particularly last sentence of Abstract).

Falnes et al. describe the ability of Tat and VP22 protein transduction domain peptides to bind to the membrane surface, but not translocating the membrane bilayer (see page 4352, Figure 2, lack of toxicity for dtA when conjugated to Tat or VP22 protein transduction domain).

Therefore, the unpredictability arises due to the differing functional effects of the conjugated polypeptide, due to the different structures of the peptides.

Consequently, there would be a large quantity of experimentation necessary to determine what structural alterations can be made without disrupting the functional effects of the individual polypeptides.

How would one of skilled in the art synthesis the conjugated polypeptides if it is unknown what peptide can be altered without affecting its function?

8.) Level of skill in the art: the level of skill in this art is high, at least that of a doctoral scientist with several years of experience in the art.

In consideration of the Wands factors, it is apparent that there is undue experimentation because of variability in prediction of outcome that is not addressed by the present application disclosure, examples, teaching, and guidance presented. Absent factual data to the contrary, the amount and level of experimentation needed is undue.

Claim Rejections - 35 USC § 102

9. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

10. Claims 31, 34, and 35 are rejected under 35 U.S.C. 102(a) as being anticipated by Navarro-Quiroga et al. (Molecular Brain Research 105: 86-97 (2002)).

Navarro-Quiroga et al. describe a fusion polypeptide comprising SEQ ID NO: 3 (GLFEAIAEFIEGGWEGLIEG). The peptide is conjugated to Vp1 nuclear localization signal of

SV40 and with a neurotensin polypeptide sequence (see page 87, Materials and methods, section 2.1).

Conclusion

11. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anand U. Desai, Ph.D. whose telephone number is (571) 272-0947. The examiner can normally be reached on Monday - Friday 9:00 a.m. - 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Kathleen Kerr Bragdon can be reached on (517) 272-0931. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

March 2, 2007

ROBERT A. WAX
PRIMARY EXAMINER